## Remarks

Rejections under 35 U.S.C. §112

Claim 1 stands rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner states that "the specification does not contain any test results or experimental data showing (that) an agent that permits the release of proteins from the endoplasmic reticulum (ER) will, in fact, alleviate or alleviating (similar to prevent) rhinosinusitis, especially in an individual not presently at risk of or predisposed to developing such disorder". Applicants respectfully disagree with the rejection of claim 1, for each of the reasons below.

Firstly, it appears that the Examiner has misunderstood the meaning of the term "alleviate" in making the rejection. As defined in *The American Heritage College Dictionary*, Second College Edition, Houghton Mifflin, Boston, 1985, "alleviate" means "to make more bearable", "to reduce", as in "taking drugs to alleviate the pain". It is thus evident that "alleviating the symptoms" of rhinosinusitis as recited in claim 1 refers to administering an agent to an individual who is already suffering from rhinosinusitis. If the individual is not suffering from rhinosinusitis then there are no symptoms to alleviate. Therefore the question of whether the specification contains data showing prevention of rhinosinusitis is not relevant to enablement of claim 1.

Secondly, regardless of whether the term "alleviate" encompasses prevention, Applicants submit that it is not necessary to provide experimental data or test results showing that an agent that permits the release of proteins from the endoplasmic reticulum (ER) will alleviate rhinosinusitis in order to demonstrate enablement of claim 1. As explained in MPEP § 2164.04, in order to make a rejection for lack of enablement, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F. 2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). Applicants submit that this burden has not been met. The claims recite a number of suitable agents, and the Examiner has not provided any evidence suggesting that these agents would not alleviate rhinosinusitis. Instead, the Examiner has merely asserted that

the specification does not contain data showing that an agent that permits release of proteins from the ER will alleviate rhinosinusitis while ignoring what the specification does in fact teach, certain aspects of which are described below.

In particular, the specification contains data showing that a variety of agents are effective in releasing proteins from the ER and that these agents alleviate features characteristic of the cystic fibrosis (CF) phenotype in tissue culture cells and in mice. See, e.g., the Examples at pp. 44-60, showing that: (i) treatment with thapsigargin, DBHQ, or cyclopiazonic acid causes increased levels of the CFTR channel in the plasma membrane of CF mutant cells and restores CFTR $Cl^-$ channel activity; and (ii) treatment with thapsigargin reverses a phenotypic defect in CF mutant mice, i.e., it corrects the nasal potential difference in these mice towards more normal values.

The specification also establishes a correlation between CF, CF mutations, and rhinosinusitis. Applicants therefore submit that absent evidence to the contrary, agents that are effective to alleviate features of CF should be accepted as being effective to alleviate symptoms of rhinosinusitis. More specifically, as indicated at pp. 2-4 of the specification, CF occurs in individuals whose genomes are homozygous for a variety of mutations in the *CFTR* gene ("CF mutations"), such that presence of these mutations in both copies of the gene causes an individual to develop CF. As further disclosed in the specification at p. 22, line 11 – 31, chronic rhinosinusitis (CRS) is almost invariably present in individuals with cystic fibrosis, and individuals who have CF mutations in only one copy of the gene generally show a significantly increased incidence of chronic rhinosinusitis relative to individuals who do not have such mutations. In other words, the presence of the mutations correlates with increased incidence of rhinosinusitis.

Since the same mutations appear to be involved in CF and development of rhinosinusitis in these individuals, CF serves as a model for rhinosinusitis. Based on this model, the ability of an agent to alleviate CF by permitting the release of proteins from the endoplasmic reticulum should be predictive of the ability of that agent to alleviate rhinosinusitis. Therefore, Applicants submit that the ability of an agent to alleviate CF serves as a model that is predictive of the ability of the agent to alleviate rhinosinusitis and should be accepted as such by the Examiner unless the Examiner has evidence that the model does not correlate. See *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436,

1441 (Fed. Cir. 1995) and *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985).

In summary, Applicants submit that the specification provides ample enablement for claim 1 since it includes data showing that various agents that permit release of proteins from the ER are effective in alleviating features of CF and it establishes a correlation between CF, CF mutations, and rhinosinusitis. Finally, Applicants would like to point out that the Examiner has already allowed claim 1 in the course of prosecution of this case. A Notice of Allowance, allowing all claims currently pending in the instant application, was mailed on 11/04/03 and the case indeed proceeded to issue as U.S. Patent No. 6,753,343. The application was withdrawn upon Applicants' petition to permit filing of an Information Disclosure Statement. Applicants have not amended any of the claims since they were allowed, and no reason has been presented why claims previously found allowable right through to issuance in a patent are now deemed not enabled. Withdrawal of the instant rejections is respectfully requested. In the event that the instant rejections are maintained, Applicants earnestly request a detailed explanation of their basis.

Claims 1 and 30-40 stand rejected under 35 U.S.C. §112, first paragraph, on the ground that the specification, while being enabling for a calcium pump inhibitor and an oligonucleotide, does not reasonably provide enablement for any and all (i) agents that permit the release of proteins from the ER; (ii) agents that decrease or inhibit the activity of UDP glucose:glycoprotein glycosyl transferase; (iii) agents that decrease or inhibit activity of the ER $Ca^{++}$ ATPase; (iv) agents that lower the concentration of $Ca^{++}$ in the ER; (v) agents that stimulate or increase IP3 receptor activity; (vi) agents that decrease or inhibit calnexin functional activity; and (vii) agents that increase or activate ryanodine receptor activity. Applicants respectfully disagree, for each of the reasons set forth below.

Firstly, the application is presumed enabled, absent evidence to the contrary. The Examiner has provided absolutely no evidence to support his assertion that the claims lack enablement. As stated by the Federal Circuit, "In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement

provided for the claimed invention." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Furthermore, according to *In re Bowen*, 492 F.2d 859, 862-63, 181 USPQ 48, 51 (CCPA 1974), the minimal requirement is for the examiner to give reasons for the uncertainty of the enablement. In the instant case the Examiner has simply stated that the claims are not enabled and provided no evidence or reasoning to suggest that this is the case.

Secondly, Applicants are not required to enable "any and all agents" that could be used to practice the claims. As the Federal Circuit has stated, "The enablement requirement is met if the description enables *any* mode of making and using the claimed invention." *Engel Industries, Inc. v. Lockformer Co.*, 946 F.2d 1528 (Fed. Cir. 1991) (emphasis added). Furthermore, "It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Applicants submit that the specification provides examples of agents in each of the categories enumerated above. In particular, the specification discloses (i) agents (e.g., thapsigargin, DBHQ, cyclopiazonic acid) that permit release of proteins from the ER, as discussed above; (ii) agents that decrease or inhibit the activity of UDP glucose:glycoprotein glycosyl transferase, e.g. an oligonucleotide, which the Examiner states is enabled (see claim 41); (iii) agents that decrease or inhibit activity of the endoplasmic reticulum $Ca^{++}$ ATPase, e.g., thapsigargin, DBHQ, cyclopiazonic acid, or an oligonucleotide (see p. 16, lines 20-23, and claim 41); (iv) agents that lower the concentration of $Ca^{++}$ in the ER. Such agents include the aforementioned agents that decrease or inhibit activity of the ER $Ca^{++}$ ATPase, since the effect of these agents is to cause a decrease in the concentration of $Ca^{++}$ in the ER.; (v) agents that stimulate or increase $IP_3$ receptor activity, e.g., adenophostin A (p. 17, lines 9-10); (vi) agents that decrease or inhibit calnexin functional activity, e.g., an oligonucleotide (see claim 41); and (vii) agents that increase or stimulate ryanodine receptor activity, e.g., ryanodine and related plant alkaloids, xanthines, 4-Chloro-m-cresol, suramin, and ditalis (*sic*) glycosides (p. 18, lines 1-2).

In summary, the Examiner has not presented any evidence to show that any of claims 1 or 30-40 lack enablement. Applicants have disclosed examples of agents that would enable each of these claims, and Applicants are not required to disclose any and all

agents that would fall within the claims. Finally, as stated above, claims 1 and 30-40 have been previously allowed and no reason has been presented why they are now deemed to lack enablement. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §112

Claims 38 and 39 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In particular, the Examiner states that claim 38 is rendered indefinite by the phrase "the agent comprises DBHQ or a derivate (*sic*) thereof". The Examiner finds it unclear whether DBHQ or a derivative thereof is combined with the agent of claim 1 or whether the agent of claim 1 is, in fact, DBHQ. With respect to claim 39, the Examiner finds it unclear whether cyclopiazonic acid or a derivative thereof or halothane or a derivative thereof is combined with the agent of claim 1 or whether the agent of claim 1 is in fact cyclopiazonic acid or halothane. Applicants submit that the language of claim 38 clearly indicates that in claim 38, the agent of claim 1 is DBHQ or a derivative thereof. Similarly, the language of claim 39 clearly indicates that in claim 39, the agent of claim 1 is cyclopiazonic acid or a derivative thereof, or halothane or a derivative thereof. For the convenience of the Examiner, claims 38 and 39 are rewritten below as they would appear in independent format, i.e., incorporating all the limitations of the claims from which they depend. The claims below are thus equivalent to pending claims 38 and 39. Applicants submit that these claims are not indefinite and respectfully request withdrawal of the rejection.

38. (Rewritten in independent format) A method of treating rhinosinusitis or alleviating the symptoms of rhinosinusitis, comprising:

providing an individual suffering from rhinosinusitis; and

administering an agent that permits the release of proteins from the endoplasmic reticulum, wherein the agent comprises DBHQ or a derivative thereof.

38. (Rewritten in independent format) A method of treating rhinosinusitis or alleviating the symptoms of rhinosinusitis, comprising:

providing an individual suffering from rhinosinusitis; and

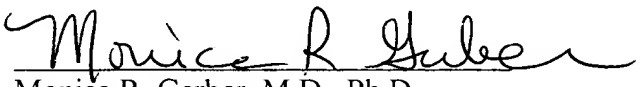
administering an agent that permits the release of proteins from the endoplasmic reticulum, wherein the agent comprises cyclopiazonic acid or a derivative thereof or wherein the agent comprises halothane or a derivative thereof.

In light of the foregoing Amendment and Remarks, Applicants respectfully submit that the present case is in condition for allowance. A Notice to that effect is respectfully requested.

If, at any time, it appears that a phone discussion would be helpful or if questions arise regarding the amendment proposed above, please do not hesitate to contact the undersigned at (617) 248-5071.

Please charge any fees associated with this filing, including fees associated with Petitions for Extension of Time, or apply any credits, to our Deposit Account No. 03-1721.

Respectfully submitted,



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Dated: January 24, 2005

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